A new catalyst-free microwave-assisted one-pot four-component synthesis of 1,4-dihydroquinolines in aqueous media

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Abstract

A novel rapid one-pot four-component reaction between resorcinol, aromatic aldehydes, malononitrile and ammonium acetate in aqueous media was performed under microwave irradiation for the synthesis of 1,4-dihydroquinoline derivatives. The main advantages of this method are the short reaction time, high yields, despite absence of any catalyst, and simple work-up.

***Keywords*:** 1,4-dihydroquinolines, Multicomponent reaction; Microwave-assisted

Introduction

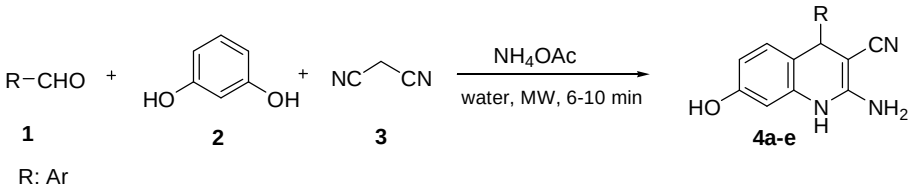
1,4-dihydroquinoline derivatives comprise a large family of medicinally important compounds. They are used in production of antihypertension, antidiabetic, and so many other drugs. [1-3] Owing to its vast medicinal utility, various methods have been adopted for the preparation of substituted 1,4-dihydroquinoline. But some of those methods still have their own limitation in terms of yields, longer reaction time, and difficult work-up. In some cases, catalysts used are harmful to environment and cannot be reused.[4] Therefore, the development of new methods for their synthesis is an area of considerable ongoing interest.

On the other hand, the development and discovery of efficient and rapid methods take into account the criterion of sustainable chemistry is of great importance for the chemists.[5] Microwave irradiation often provides many chemical reactions with attributes, such as enhanced reaction rates, remarkably decreased reaction time, increased yield, and

easier workup and several eco-friendly advantages.[6-9] Also multicomponent reactions (MCRs) have recently taken a new dimension in organic synthesis.[10] The usefulness of MCRs is even greater when they give access to useful heterocyclic scaffolds for medicinal chemistry.[11] One such significant scaffold is the quinoline nucleus which is key constituent of a wide range of both natural and synthetic bioactive compounds. According to the current synthetic requirements, environmentally benign multi-component procedures employing microwave methodology are particularly welcome.

Results and discussion

In view of the potential medicinal importance of the products and considering the limitations of the existing methods, we have investigated a catalyst free one-pot simple and efficient procedure for the rapid preparation of substituted 1,4-dihydroquinolines via a four-component reaction under controlled microwave conditions. We found that in the absence of any catalyst, a mixture of aromatic aldehydes, resorcinol, malononitriles, and ammonium acetate (molar ratio 1:1:1:1.5) in water under microwave irradiation for 6-10 min, afforded **4a-e** in high yields (**Scheme 1**). The results are summarized in **Table 1** and reveal that the aldehydes containing electron withdrawing groups undergo reaction sluggishly with diminution of the product yield.

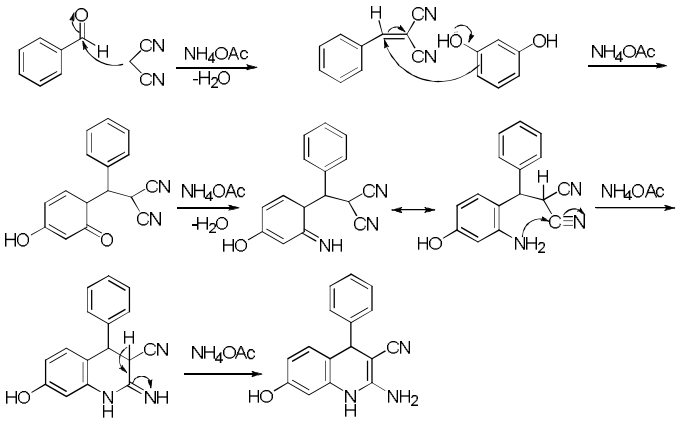


Scheme 1. Synthesis of 1,4-dihydroquinoline derivatives from aldehydes, resorcinol, malononitrile and ammonium acetate under MW irradiation

Table 1. Four component synthesis of 1,4-dihydroquinoline derivatives

Entry	R	Time (min)	Yield (%)	Mp (˚C)
1	4-BrC_6H_4	8	80	239-241
2	4-$OCH_3C_6H_4$	7	86	>300
3	4-OHC_6H_4	6	84	>300
4	4-$CH_3C_6H_4$	10	75	>300
5	4-(N,N dimethyl)-C_6H_4	6	95	166-168

Finally, we turned our attention to the mechanism of the reaction. A possible reaction mechanism for the formation of 2-amiono-3-cyano-7-hydroxy-1,4-dihydroquinoline was proposed (**Scheme 2**).



Scheme 2. Proposed mechanism for preparation of 2-amiono-3-cyano-7-hydroxy-1,4-dihydroquinoline

Conclusion

In conclusion, a novel efficient, atom-economical, catalyst-free, and simple method for the preparation of various 1,4-dihydroquinoline derivatives via a microwave-assisted one-pot four-component reaction using readily available starting materials was performed. Prominent among the advantages of this new catalyst-free method are the operational simplicity, short reaction time, good yields, and the easy workup procedures employed. To the best of our knowledge, this new procedure provides the first example of a catalyst-free synthesis of 1,4-dihydroquinoline derivatives.

Experimental Section

General

Chemicals were purchased from Fluka, Merck, Riedeldehaen AG and Aldrich chemical companies. All melting points were measured with a Branstead Electrothermal melting point apparatus and uncorrected. A household microwave with maximum power of 900 W was used in this study.

Experimental procedure

A mixture of aldehydes **1** (2 mmol), resorcinol **2** (2 mmol), malononitrile **3** (2 mmol), and ammonium acetate (3 mmol) in water (20 ml) was irradiated under MW at low power (300 W) for an appropriate time (**Table 1**). After completion of reaction, as indicated by TLC, the reaction mixture was filtered, washed with water and recrystallized from ethanol to afford the pure product. All the products were fully characterized by their melting points and spectral data (IR, ^{1}HNMR, ^{13}CNMR).

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